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Breathtaking! About the comparison of the subjective sensations of pain and dyspnea

With interest we read the contribution of Nishino and colleagues [6] in this issue of *Pain*. By comparing subjective responses to cold pressor-induced pain and to an end-expiratory breathhold, they demonstrated that participants' pain threshold was correlated to their dyspnea threshold, whereas tolerance levels for pain and dyspnea were uncorrelated. We feel that contributions like this are valuable. Similarities between the sensations of pain and dyspnea – both highly unpleasant and together with fatigue the most commonly reported sensations in primary care – have been described previously, but more research is needed to further shape our understanding of how exactly pain and dyspnea are akin. Furthermore, whereas the biopsychosocial model can be viewed as a giant leap forward in the understanding of pain suffering, much is to be learned from pain research to better understand and target dyspnea suffering. Specific aspects of the methodology used by Nishino et al. [6] may, however, leave room for alternative explanations of their results.

First, the validity of using the subjectively rated sensation of 'discomfort' to determine participants' threshold and tolerance may be debatable. Although it is a solution that allows for the use of one and the same scale in both challenges, participants may have rated other sensations than strictly pain and dyspnea. For example, the cold pressor task may evoke cold sensations that are uncomfortable before they get painful. Whereas the authors explicitly instructed participants to disregard the sensations that were experienced before the start of the breathhold, no such instructions were given before the cold pressor trial. Given this, the authors may have assessed different types of sensory thresholds by operationalizing the pain threshold and the dyspnea threshold similarly as "a sudden rise in VAS above 0".

Moreover, other factors may have influenced participants' reports of discomfort. For example, we have shown that negative affectivity (NA), a factor closely related to trait anxiety, is associated with increased symptom reporting in healthy individuals and in patients with asthma [2,3,7,9], especially when sensations are ambiguous or low in intensity and not when sensations are straightforward and strong [1,5]. Could it be that the correlation between the pain threshold and the dyspnea threshold in the Nishino et al. study [6] is due to a general tendency of participants high in NA to interpret ambiguous sensations that occurred early on in both challenges as uncomfortable? If so, this would argue against a shared mechanism for pain and dyspnea as specific sensations; it would rather add to the evidence that the general tendency of individuals high in NA is to negatively interpret sensations, independent of the source of these sensations.

This alternative explanation also places constraints on Nishino et al.'s assumption that "it is evident that the threshold is closely associated with the sensory-discriminative dimension". Similarly, assuming that "Since the tolerance appears to be closely related to behaviors of escape and avoidance, the tolerance may be associated more closely with the affective dimension than the threshold" may not be warranted for dyspnea. Based on previous research in our own lab, we would argue that the dyspnea threshold – as measured by Nishino et al. – is more strongly influenced by the affective dimension than the tolerance. Considering that in pain, psychological factors mainly influence tolerance levels rather than thresholds [e.g. 4], this may be an important difference between pain and dyspnea that requires further investigation.

Second, the results from the Nishino et al. study also seem conflicting with the results of Schön et al. [8] who report a relationship between perceived pain and dyspnea in the unpleasantness dimension, but not in the intensity dimension. Whereas Schön et al. [8] used inspiratory resistive loading, which induces a sensation of loaded breathing, requiring more work and effort to breathe, this is different from breathholding, which evokes feelings of air hunger, as used by Nishino et al. [6]. These differences in participants' subjective experiences may have, to a certain extent, influenced the results of both studies. However, the different results found in both studies cannot be explained by the *duration* of the respiratory challenge: Schön et al. used inspiratory resistive loading for 1 min, which is on average only a few seconds longer (not shorter, as Nishino et al. argue) than the breathhold time in the Nishino et al. study.

Notwithstanding, the duration of the cold pressor task in both studies was – especially in the pain-tolerant group in the Nishino et al. study – about three times the duration of the breathhold time. Using challenges of similar duration for the induction of pain and dyspnea may be advisable when one wants to compare how these sensations are subjectively perceived. Whereas shorter challenges may be advisable to establish 'pure' (i.e., physiological) thresholds and tolerances, long(er) challenges may be more suited to investigate the influence of psychological factors and individual differences on the perception of pain and dyspnea. These influences would then be the strongest during earlier stages of the challenge [5]. Moreover, it should be noted that there are a number of physiological parameters related to an individual's body composition (e.g., age, gender, weight, height, but also diffusion capacity of the lungs) that influence breathholding time to a great extent. We are somewhat surprised to see that individual differences on these variables were not controlled for by the authors.

Third, at a more basic methodological level, one could even argue that the use of between-person correlations to quantify a within-subject relationship is amenable to improvement and within-person correlations are preferable to investigate within-person relationships. One methodology to investigate the respiratory threshold and tolerance that (1) allows for repeated – or even continuous – ratings of subjective experiences and (2) induces a more gradual increase in discomfort similar to that experienced in the cold pressor task may be the rebreathing test [10,11]. In the rebreathing test, participants breathe into a closed circuit which, compared to end-expiratory breathholding, induces a more gradual increase in hypercapnia-induced air hunger and allows a more fine-grained analysis of an individual's sensitivity, as well as the influence of psychological factors.

We hope that these suggestions may contribute to a methodologically sound approach to study the similarities and differences between pain and dyspnea.

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Reply to the letter to the editor

We appreciate the comments and suggestions made by Dr. De Peuter and colleagues. Since they expressed several concerns about the methodology used by us, we would like to comment upon several points related to their concerns.

First, they are concerned about the validity of using the subjectively rated sensation of pain and dyspnea. They suggested the possibility that the cold-pressor test might have evoked cold sensations that are uncomfortable before they get painful. Although there might be different types of sensory thresholds during cold stimulation, pain induced by the cold-pressor test is not an ambiguous sensation and it is unlikely that the participants are unable to distinguish the painful sensation from other uncomfortable sensations. In our study, the subjects were given a short training period to accustom them to the use of the VAS both for pain and dyspnea so that the subjects were able to rate accurately the sensations of pain and dyspnea. In addition, the short training period can contribute to an attenuation of anxiety. We believe that such training period is quite useful and important in conducting the experiments that produce uncomfortable sensations such as pain and dyspnea. Our assumption that the threshold of dyspnea is closely associated with the sensory-discriminative dimension while the tolerance of dyspnea is closely associated with affective dimension is based on the results of our previous study [2] in which it has been shown that psychological factors mainly influence tolerance rather than threshold of dyspnea.

Second, a simple comparison of our results [4] with the results of Schön et al. [6] may not be valid since the methods of inducing dyspnea are different in these two studies. Obviously, the quality and quantity of dyspnea produced by an end-expiratory breathhold used in our study [4] are quite different from those produced by a 1-min inspiratory resistive loading in the study of Schön et al. [6]. In addition, the effect of psychological factors on different types of dyspnea induced in the two studies may be different. As suggested by Dr. De Peuter et al., using challenges of similar duration for the induction of pain and dyspnea may be important for comparison of pain and dyspnea. Another important point related to the given duration of pain and dyspnea is that the variability in individual differences for pain and dyspnea responsiveness should be small. In this context, the cold-pressor test used in our study may not be a suitable test since many participants reach the cut-off limits before reaching the tolerance point. In future studies different pain stimulation modalities other than the cold-pressor test should be tested.

Finally, Dr. De Peuter et al. suggested the use of rebreathing test as a substitute for breath-holding test. We agree that the rebreathing test has the advantage of causing a gradual increase in respiratory discomfort. But we should keep in mind that it has also disadvantages. One major disadvantage is that the rebreathing test without constrained rate and tidal volume (free breathing) causes a very slow and weak increase in air hunger sensation, probably due to dyspnea-relieving effects of pulmonary and chest wall mechanoreceptors [1]. Thus, it is rather difficult to obtain the tolerance value by using the rebreathing test. The effect of increasing CO_2 on the central nervous system is another confounding factor that may affect the subjective evaluation of dyspnea. Another disadvantage of using the rebreathing test is that rebreathing may attenuate the activities of upper airway receptors including the cold receptors [5], causing an increase in dyspneic sensation. There is some evidence that the intensity of dyspnea can be altered in response to stimulation and inhibition of the upper airway receptors [3,7,8].

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